REMARKS

In the outstanding Office Action, claims 1-23 were presented for examination. Applicant notes with appreciation the apparent allowability of claims 13, 14, 16-19 and 23 which were not subject to rejection. However, Claims 1-5, 11 and 12 were rejected on formal grounds under 35 U.S.C. §112. In addition, rejection was advanced on the basis of 35 U.S.C. §102 against claims 1-2, as being anticipated by a reference to Montal et al.

The Office Action has been most carefully studied. In this amendment applicant has canceled certain claims without prejudice, and has amended others. Accordingly, as will be discussed in detail below, it is believed that the application is clearly in condition for allowance.

Declaration with New Power and Correspondence address

Pursuant to the Office's requirement, a new declaration is filed herewith. It is respectfully requested that the new power and correspondence address contained therein be promptly entered. The priority and PCT information have been listed in the proper sections of the declaration.

Claim Amendments

Minor, inconsequential amendments have been made to Claim 1 to adopt the Examiner's suggestion regarding "SEQ ID NO:" and otherwise for readability and to Claim 12 to adopt the definite article, as called for by the Examiner. The choice of article to introduce a dependent claim is believed immaterial. These amendments are made without narrowing or to make explicit language that was previously inherent.

Claim Rejections - 35 U.S.C. §101 "Hand of man"

Base claims 1 and 11 have been amended to qualify the recited peptides as being "synthetic" so as to exclude nonstatutory subject matter, pursuant to the Office's helpful suggestion, to thereby overcome the rejection under 35 USC §101. No surrender of synthetic equivalents of the claimed materials is intended.

Claim Rejections - 35 U.S.C. §112 First Paragraph

Claim 5 the only claim rejected under 35 U.S.C. §112 for alleged lack of enablement, has been canceled.

Claim Rejections - 35 U.S.C. §112 Second Paragraph

With regard to the rejection of claim 2, it is respectfully pointed out that base claim 1 is not limited to a specific stereoisomery. Accordingly, claim 2 is believed definite. By virtue of claim 1 being directed to a synthetic peptide, a person skilled in the art will understand that its amino acid residue components may have either an L- or a D-stereoisomeric configuration. Claim 2 has been amended to improve the language, without narrowing and specifically recites the L- or D-stereoisomers as alternatives.

Claim 15 has been amended, without narrowing, by making explicit matter which was inherent to recite the outcome of "reducing or eliminating" with regard to the facial wrinkles treated. The phrase "and/or" is believed to be acceptable and to clearly call for either one or both as three permissible alternatives. Nevertheless, to avoid unnecessary issues, and for other reasons, claim 15 has been limited to wrinkle treatment, without excluding that treatment of facial asymmetry might also be effected. New claim 24 has been added directed to the subject matter of the first alternative limb of previous claim 15, namely reducing or eliminating facial asymmetry, again without excluding that treatment of wrinkles might also be effected.

Claim Rejections - 35 U.S.C. §102(b) Anticipation

Turning now to the rejection of claims 1 and 2 as anticipated by Montel et al., (WO97/34620) Claims 1 and 2, as now written are believed clearly and patentably distinguished from Montal et al., or any other art known to applicant.

Montal et al. discloses the SNAP-25 protein and fragments thereof which are disclosed to inhibit the secretion of neurotransmitters from synaptic vesicles. However, Montal et al. clearly indicates that limitations to the fragments that can be used to achieve the effect:

> *"the ESUPs [peptides] of the invention comprise synthetic and purified peptide fragments which correspond in primary structure to peptides which serve as binding domains for the assembly of a ternary protein complex"* (page 3, lines 1-4 and page 12, lines 3 to page 13, line 6).

Montal et al.'s peptides are derived from a specific part of SNAP-25, which is defined in the document as SEQ.ID. NO.4 depicted in Figure 3, and which corresponds to the C-terminal domain of SNAP-25. Alternatively the peptides that can be used are the products of BoTx and TeTx proteolytic cleavage of SNAP-25 and VAMP-2 (page 3, lines 5-8 and 15-20). As can be seen from figure 3 where they are depicted and from page 12, lines 3-12, these peptides also belong to the C-terminal domain of SNAP-25.

Furthermore, the disclosed peptides have a specific size limit:

> *"for optimum activity, ESUPs of the invention have a minimum length of about 20 amino acids and a maximal length of 28 amino acids"* (page 3, lines 8-9), see also page 11, lines 5-11.

Thus the subject-matter of present claim 1 is clearly distinguished from Montal et al. in the first place because Montal et al. does not disclose the specific peptide fragments of SEQ ID. No 2 and SEQ ID. No 3. In addition, applicant's claimed fragments have less than 20 amino acids, the lower size limit of Montal et al.'s disclosed fragments. For these reasons alone, claim 1 is clearly and patentably distinguished from Montal et al. Still further reason for patentability is provided, however, in that

applicant's claimed peptide fragments derive from the N-terminal domain of SNAP-25, not the C-terminal domain as disclosed by Montal et al.

Though not directly relevant to the issue of lack of anticipation under 35 USC §102, it is noted that one problem solved by applicant's claimed invention is to provide small peptides which inhibit neuronal exocytosis as is described in applicant's specification.

Montal et al. provides no clue that short peptides outside the substrate binding domain of SNAP-25 and which are not close to, nor contain the cleavage regions by *Clostridium* neurotoxins could act as inhibitors of exocytosis. On the contrary, the only peptide described in Montal et al. outside this binding domain is SEQ.ID.NO.11 (49-MLDEQGQLER-59), which does not affect Ca^{2+}-dependent exocytosis and, in consequence, cannot act as an inhibitor of neuronal exocytosis (see page 23, lines 18-20). The person skilled in the art, reading Montal et al., will be faced with a technical prejudice against using short sequences and against exploring sequences outside the substrate binding domain.

Furthermore, similar to other modular proteins such as receptors, transcription factors, protein anchors or cytoskeletal proteins, there is no reason to believe that the function of SNAP25 C-terminus can be attributed to the N-terminus of the protein, since different protein domains may be involved in distinct structural and or functional roles. For instance, the C-terminus domain of the p75 neurotrophin receptor most clearly illustrates that modular organization of proteins give rise to distinct functions. Hence, depending on which region of the p75 C-terminus is targeted, either cell survival or death may be obtained. The pathways to survival or death may involve different molecular events depending on the protein motif targeted [Roux, P.P. and Barker, P.A. (2002) "Neurotrophin signalling through the p75 neurotrophin receptor" *Prog. Neurobiol.* **67**, 203-233; Hempstead, B.L. (2002) "The many faces of p75NTR" *Curr. Opin.*

Neurobiol. **12**, 260-267]. It cannot be anticipated that peptides mimicking a particular protein domain will exhibit the same function as those patterned after a different motif of the protein.

Therefore, starting from Montal et al. it would not be at all obvious for the person of skill in the art to select a peptide shorter than 20 amino acids from the N-terminal domain of SNAP-25 (outside the binding domain of SNAP-25) for the inhibition of the secretion of neurotransmitters from synaptic vehicles.

The subject-matter of applicant's claims 1 and 2 can solve the problem posed as for example is shown by Example 1.2.1 of applicant's specification which demonstrates that the sequences of the invention block the catecholamine release from detergent-permeabilized chromaffin cells and as such can act as inhibitors of neuronal exocytosis.

The specification also shows that mixtures of the peptides of the invention with sequences derived from the C-terminus of SNAP-25 can produce an unexpected increase in their respective inhibitory activity, i.e. there can be a potentiation of their activity as compared to that shown by the individual peptides. The synergy in the activity notably substantiates the distinct mode of action of both types of peptide sequences.

Applicant has surprisingly found that requirements of a coiled-coil folding as proposed by Montal et al. are not enough for activity of peptides smaller than 20 amino acids. This is corroborated by the fact that SEQ.ID.NO.11 of Montal et al. shows almost 100% of coiled-coil structure in the COILS software prediction plot (Figure 6A of Montal et al.) but does not show any activity.

In summary, the present invention solves the previously stated problem of providing small peptides which inhibit neuronal exocytosis in a manner that is not considered, disclosed or even remotely suggested in Montal et al. Accordingly, reconsideration of the rejection and allowance of claims 1-2 are respectfully requested.

Allowable Claims

It is noted that claims 13, 14, 16-19, and 23 were not subject to rejection. Accordingly, the informalities having been removed, allowance of these claims together with claims 1-5, 11, 12, 15 and new 24, discussed above, is believed proper.

In view of the above amendments and the discussion relating thereto, it is respectfully submitted that the instant application, as amended, is in condition for allowance. Such action is most earnestly solicited. If for any reason the Examiner feels that consultation with Applicant's representative would be helpful in the advancement of the prosecution, they are invited to call the telephone number below for an interview.

Respectfully submitted,

By: _____

Anthony H. Handal
Reg. No. 26,275 Ph: (212) 536-4870
Roger Pitt
Reg. No. 46,996 Ph: (212) 536-4867

KIRKPATRICK & LOCKHART LLP
599 Lexington Avenue (32nd Floor)
New York, NY 10022-6030

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September 24, 2004

Anthony H. Handal
Reg. No. 26,275
Roger Pitt
Reg. No. 46,996